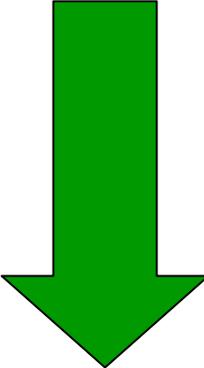
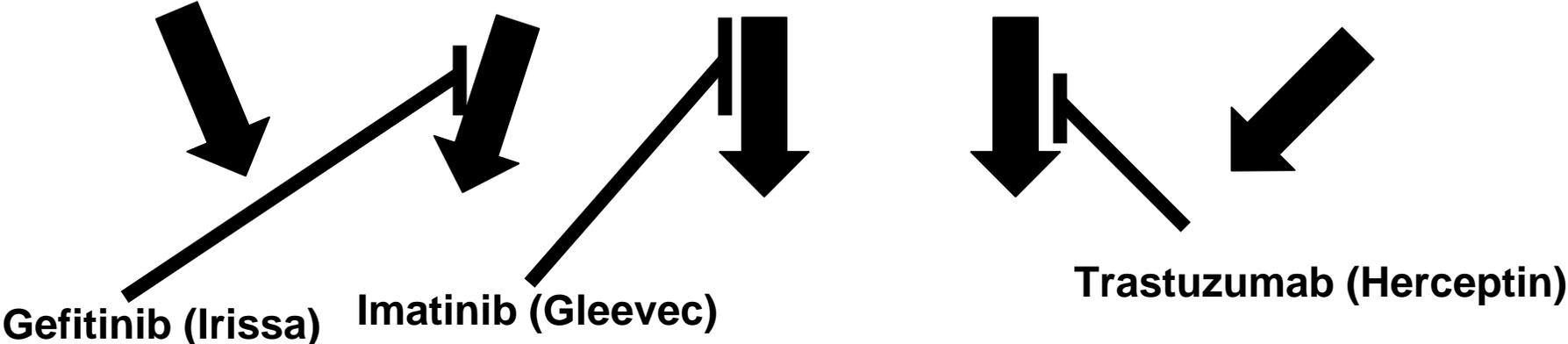


# Drug Discovery

- **Identify Molecular Targets**
  - an “Achilles Heel”
- **Validate Molecular Targets**
- **Synthesize and Test Compounds**

# Growth Factor–Growth Factor Receptor<sub>1,2,3...i</sub>

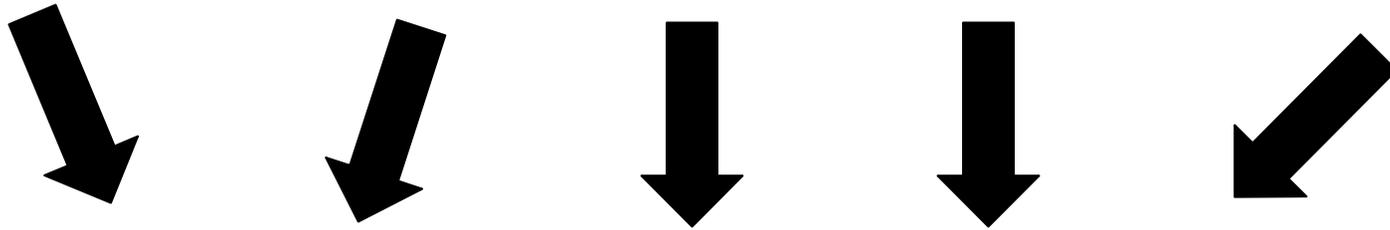
**EGF**      **PDGF**      **HER-2**



# Cancer

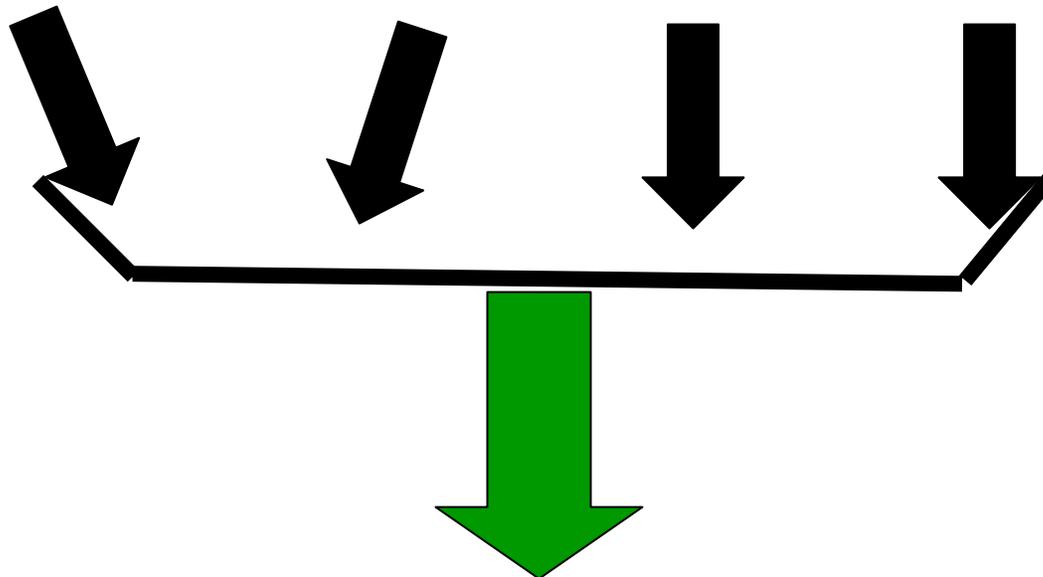
**Growth Factor–Growth Factor Receptor<sub>1,2,3...i</sub>**

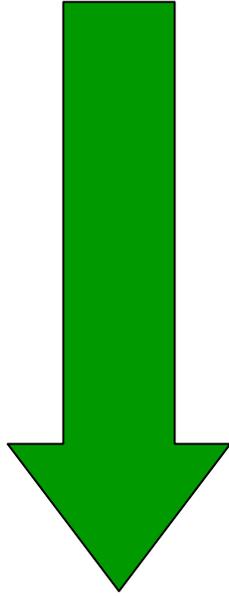
**EGF, IGF, HER-2, ...**



**Signal transducer<sub>1,2,3...k</sub>**

**Ras, tyrosine kinase, ...**





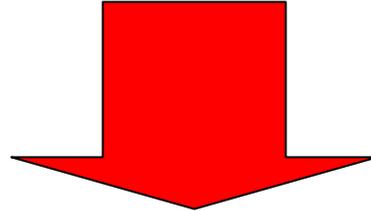
**Translation Initiation Factor**

**4F**

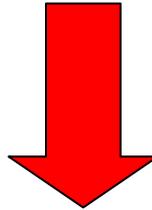
**A critical point of convergence**

# Principle of convergence

**300 cancer related genes**



**100 cancer related transcripts**

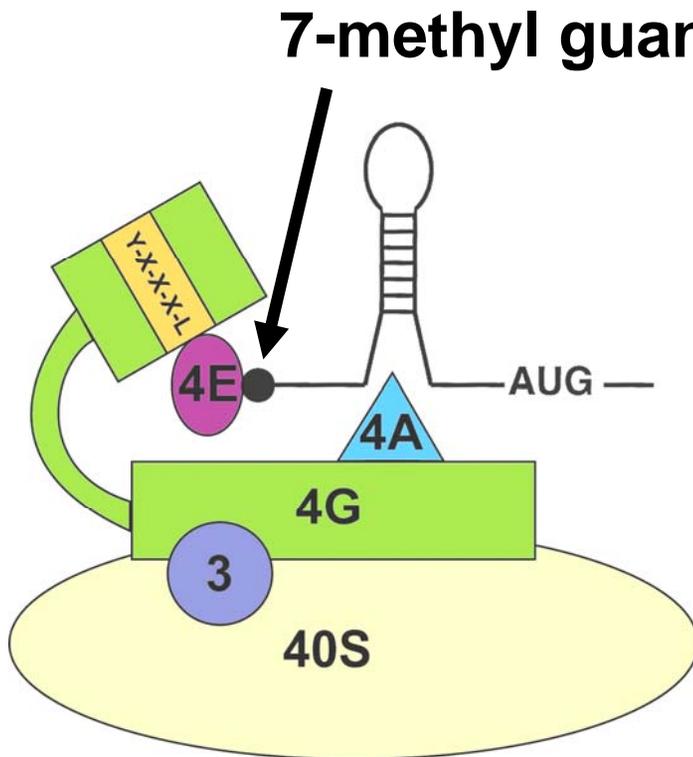


**10 cancer related pathways**



**eIF4F**

# The eIF4F Translation Initiation Complex

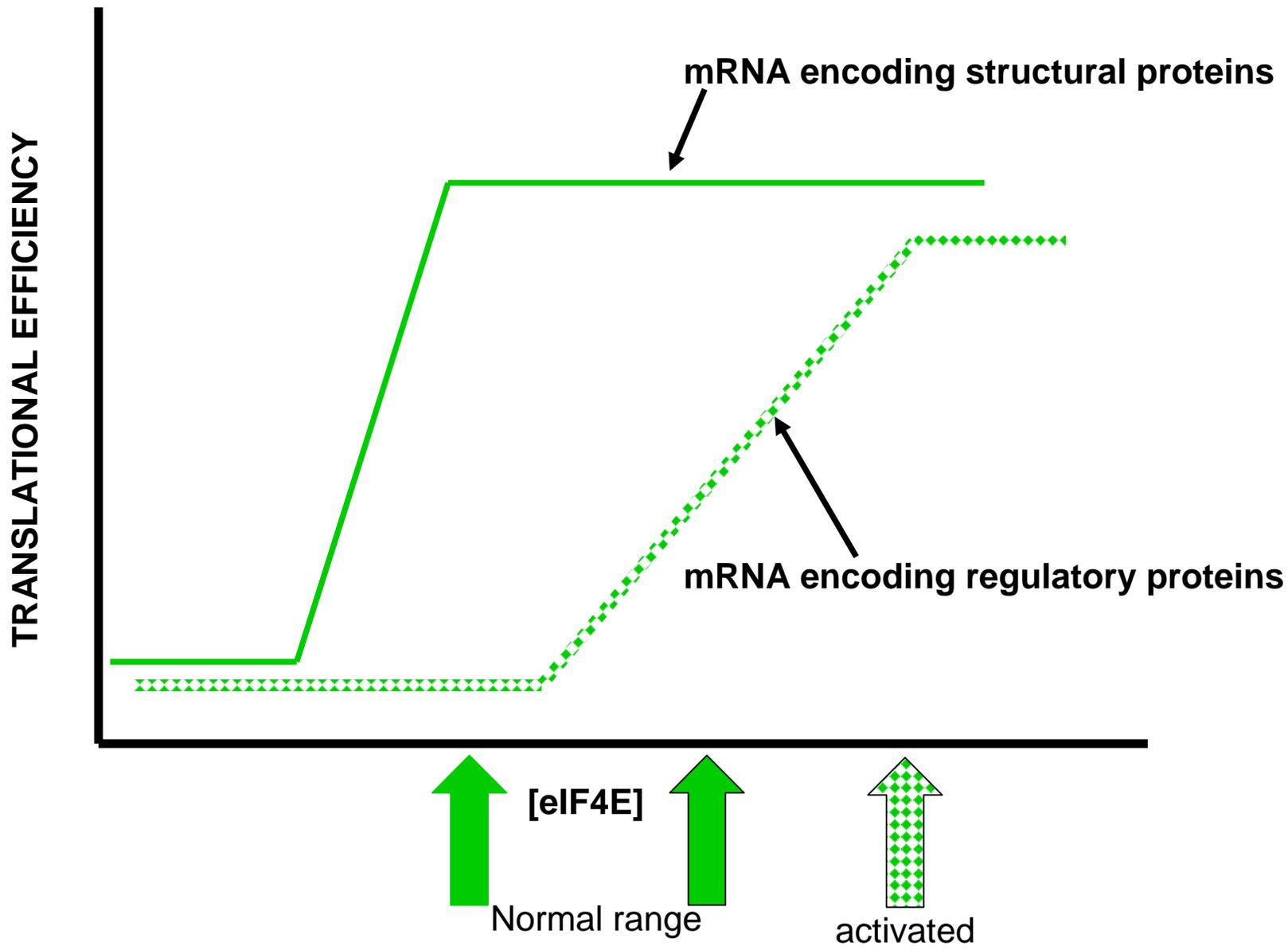


**Limiting component = 4E**

**Critical step = association of 4E with the mRNA cap**

# How does constitutive activation of the translational machinery so fundamentally alter cell function?

- **Not all transcripts are equally appealing to the protein synthesis machinery**
  - Thermodynamic constraints
  - User codes
- **Those encoding growth factors, their receptors, cyclins, antiapoptotic proteins and angiogenic factors enjoy a selective increase in translational efficiency**



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 ? eIF4F

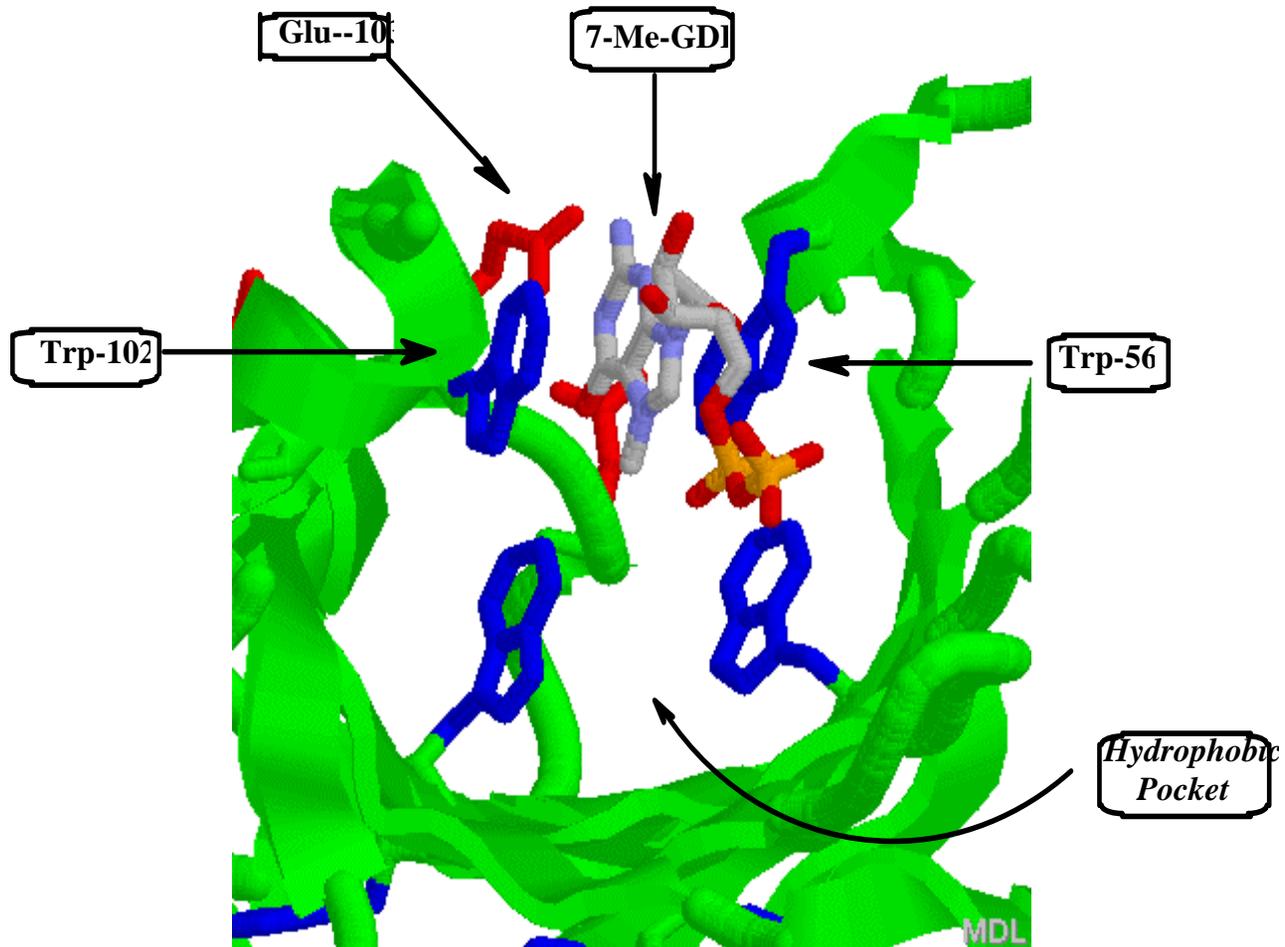
Achilles often feared that his weakness  
would be discovered.

# Is eIF4F a good molecular target?

- ☀ eIF4F is “**locked on**” in cancer 
- ☀ enforced activation of eIF4F is sufficient to confer normal cells with autonomy
- ☀ reversal of the locked on state in cancer eliminates autonomy and tumorigenicity 

and...

# ☀ The molecular target has a known structure



# Drug Discovery

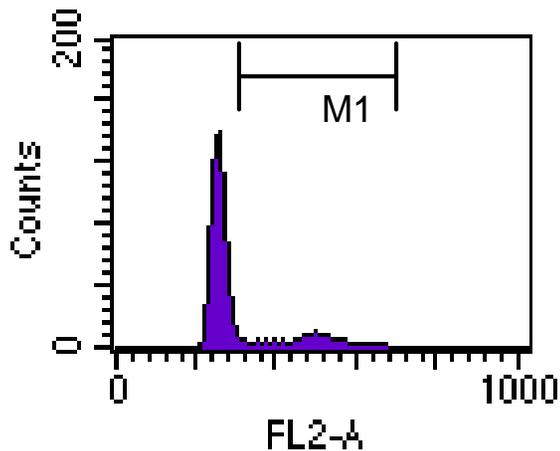
- **Identify Molecular Targets**
  - an “Achilles Heel”
- **Validate Molecular Targets**
- **Synthesize and Test Compounds**

**When eIF4F is locked  
in the **on** position, new  
biological properties  
emerge**



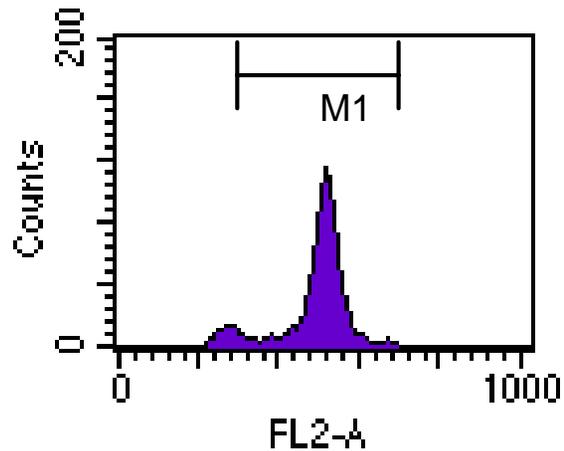
# Locking eIF4F on: Proliferative autonomy

**0.1% FCS**



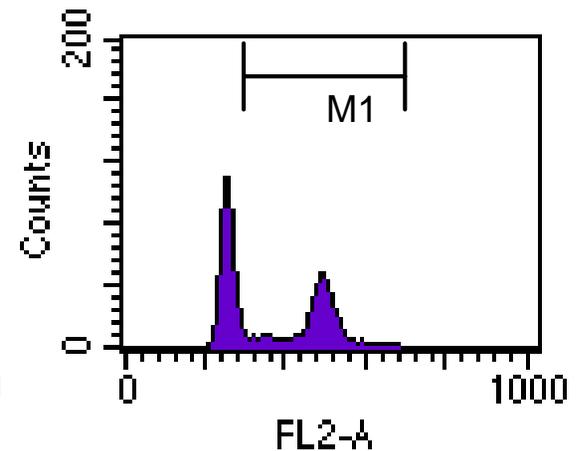
**9.8%**

**10% FCS**



**93.5%**

**0.1% + Mif**

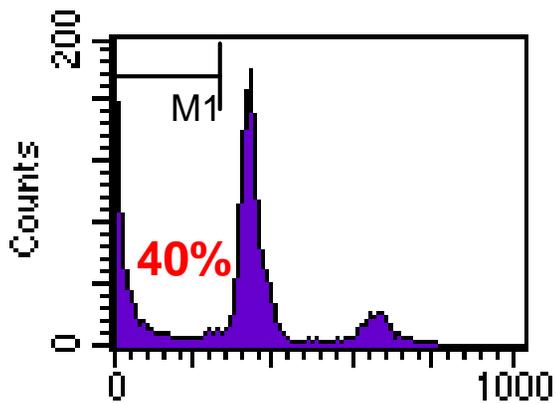


**45.8%**

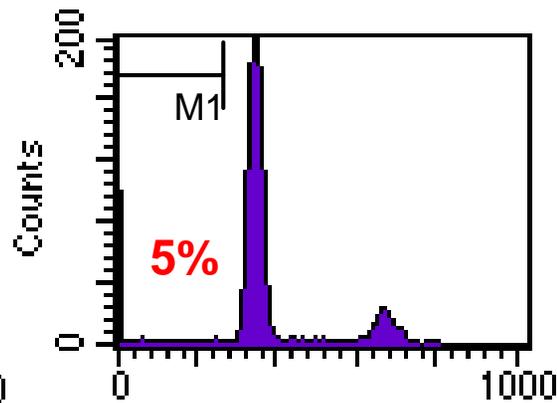


# Locking eIF4F on: survival autonomy

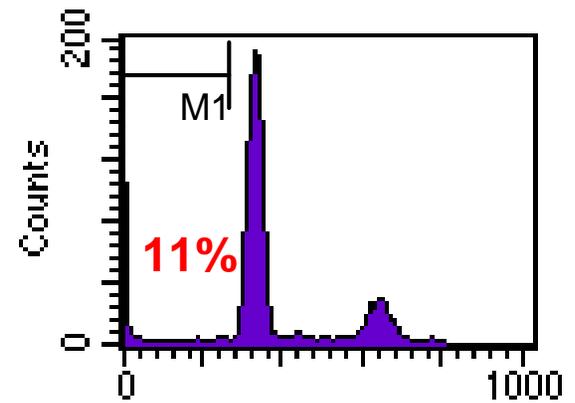
0.1% FCS



10% FCS



0.1% + Mif





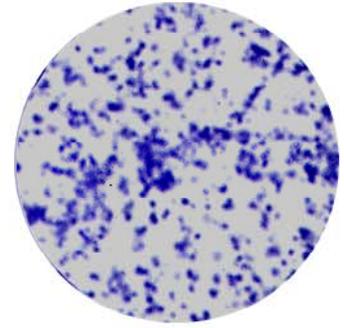
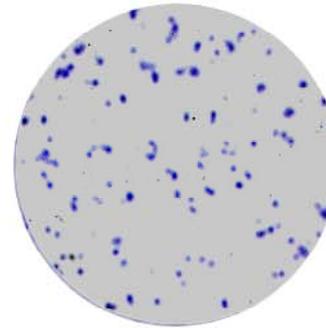
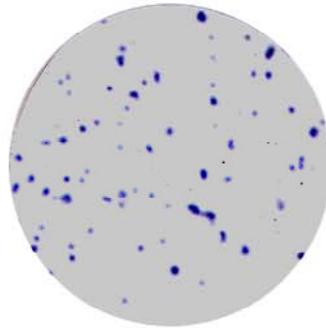
# Locking eIF4F **on**: epithelial cell colony formation and anchorage independent growth

NT

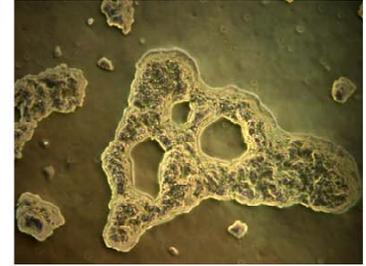
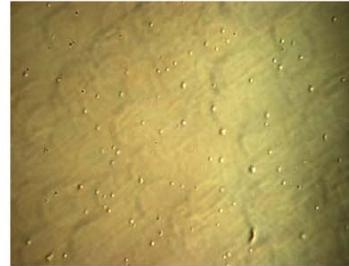
Vec

4E

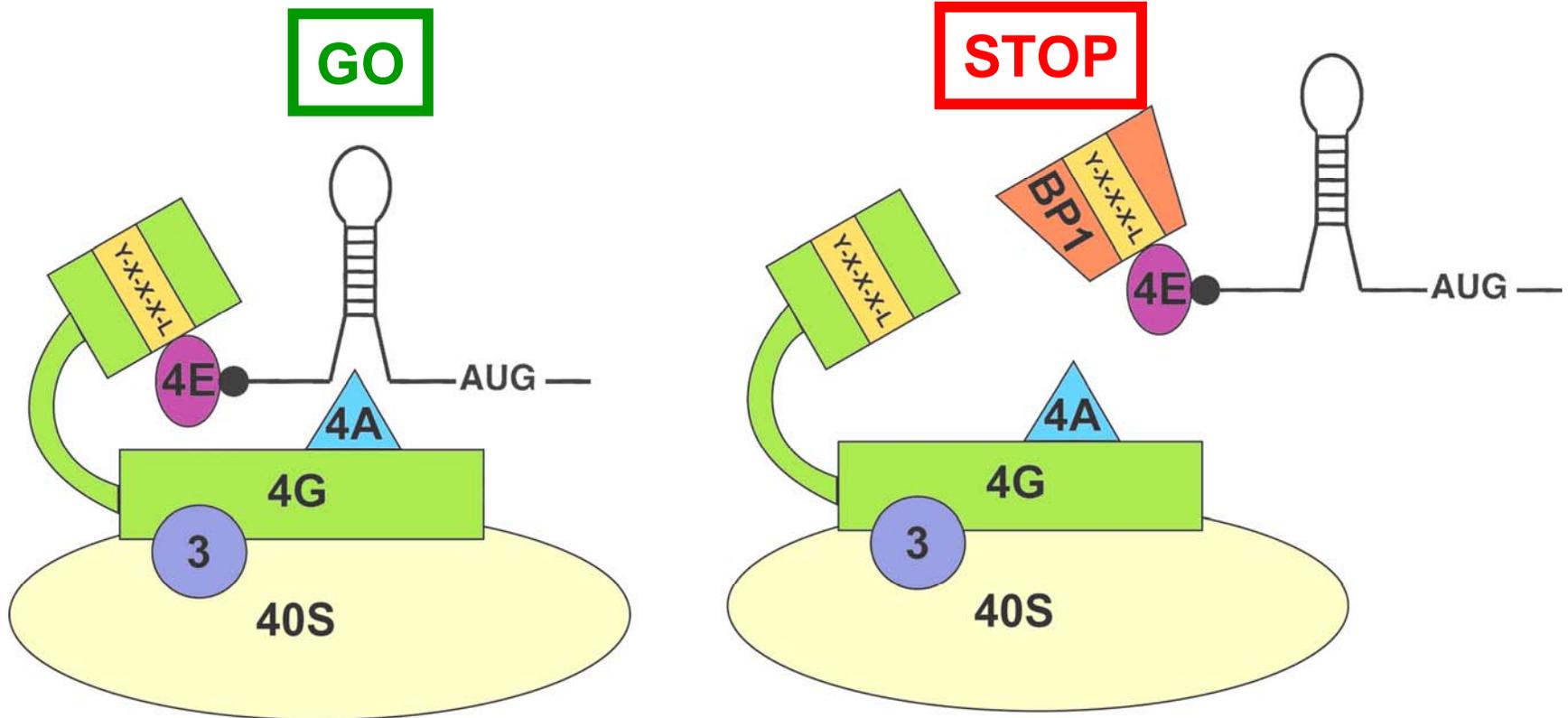
Plastic



Soft agar

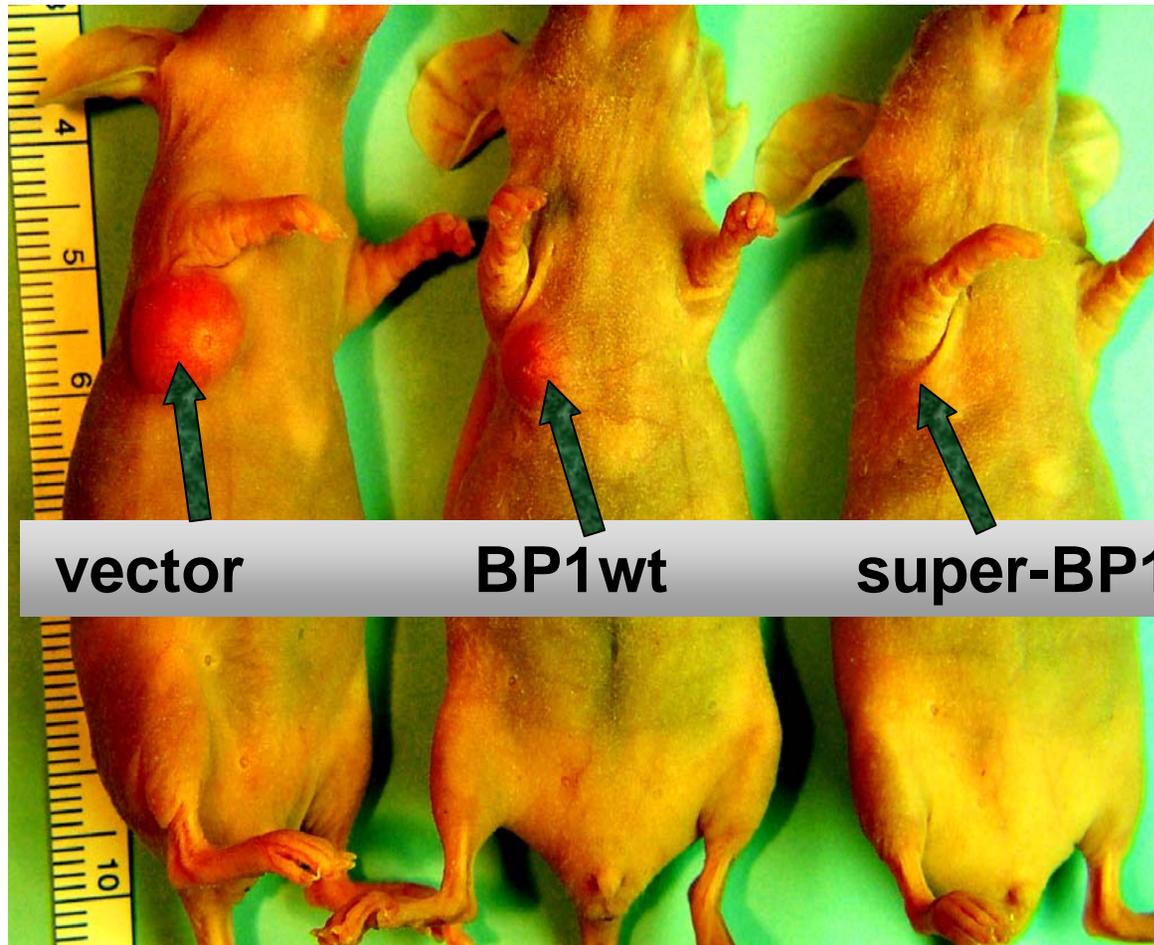


# The eIF4F Translation Initiation Complex





# Unlocking eIF4F inhibits breast carcinoma



**vector**

**BP1wt**

**super-BP1**

# **Won't inhibiting protein synthesis kill normal cells?**

- **Normal cells comfortably recalibrate their protein synthetic rate over a very wide physiological range without ill effects.**
- **Cancer cells have their translational machinery locked on; reestablishing normal levels of translation eliminates autonomy and tumorigenicity**

# Drug Discovery

- **Identify Molecular Targets**
  - an “Achilles Heel”
- **Validate Molecular Targets**
- **Synthesize and Test Compounds**

# University of Minnesota Cancer Center

Medical School

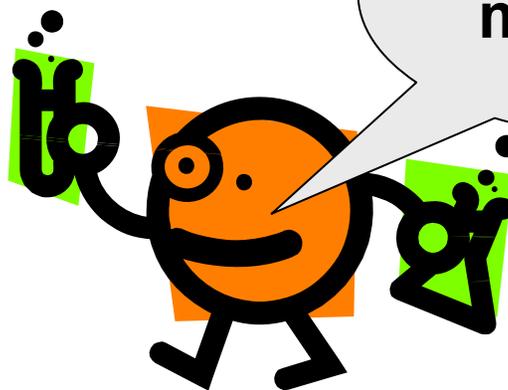
Go for it



Polunovsky and Bitterman

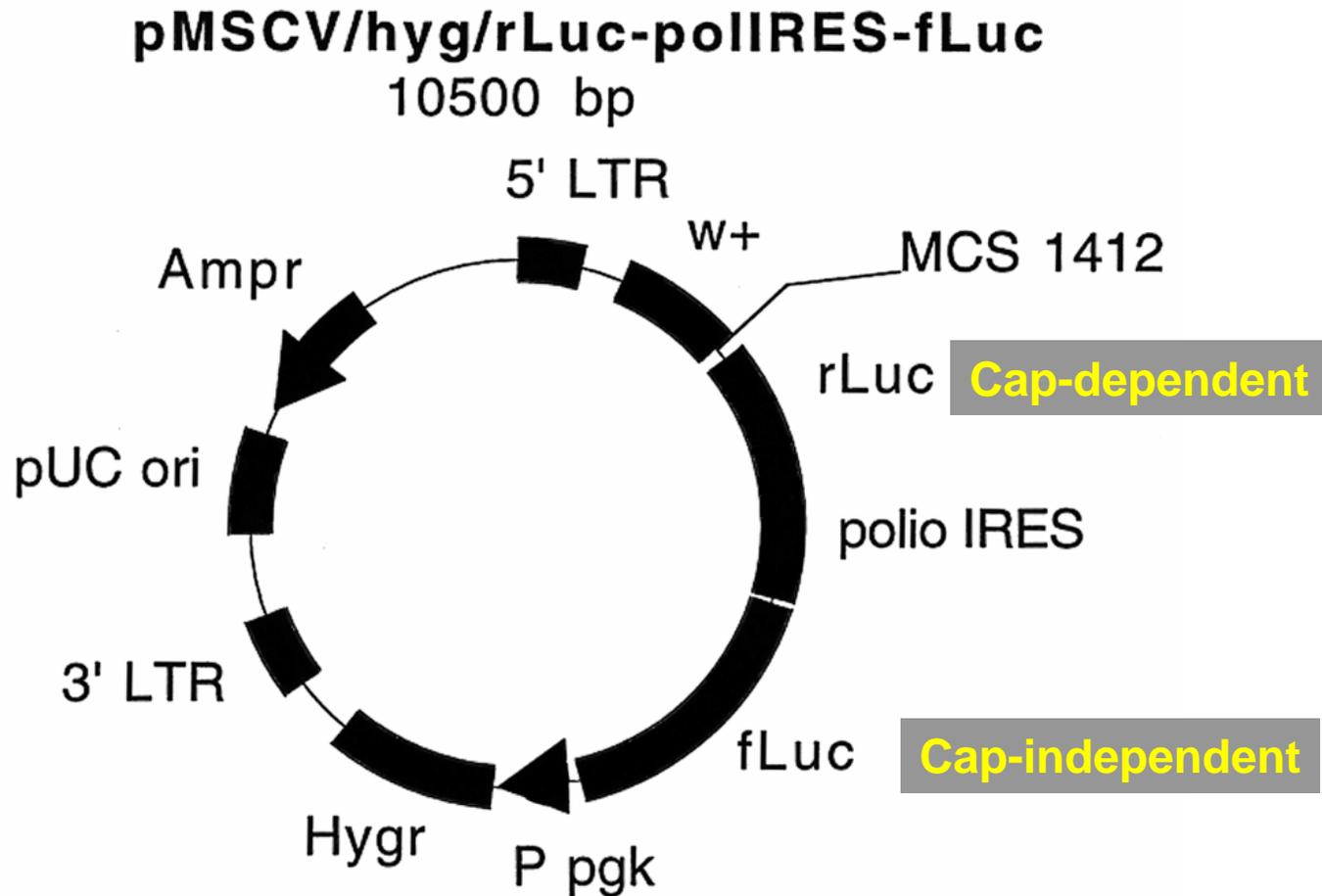
College of Pharmacy  
Medicinal Chemistry

I can hit the  
molecular  
target

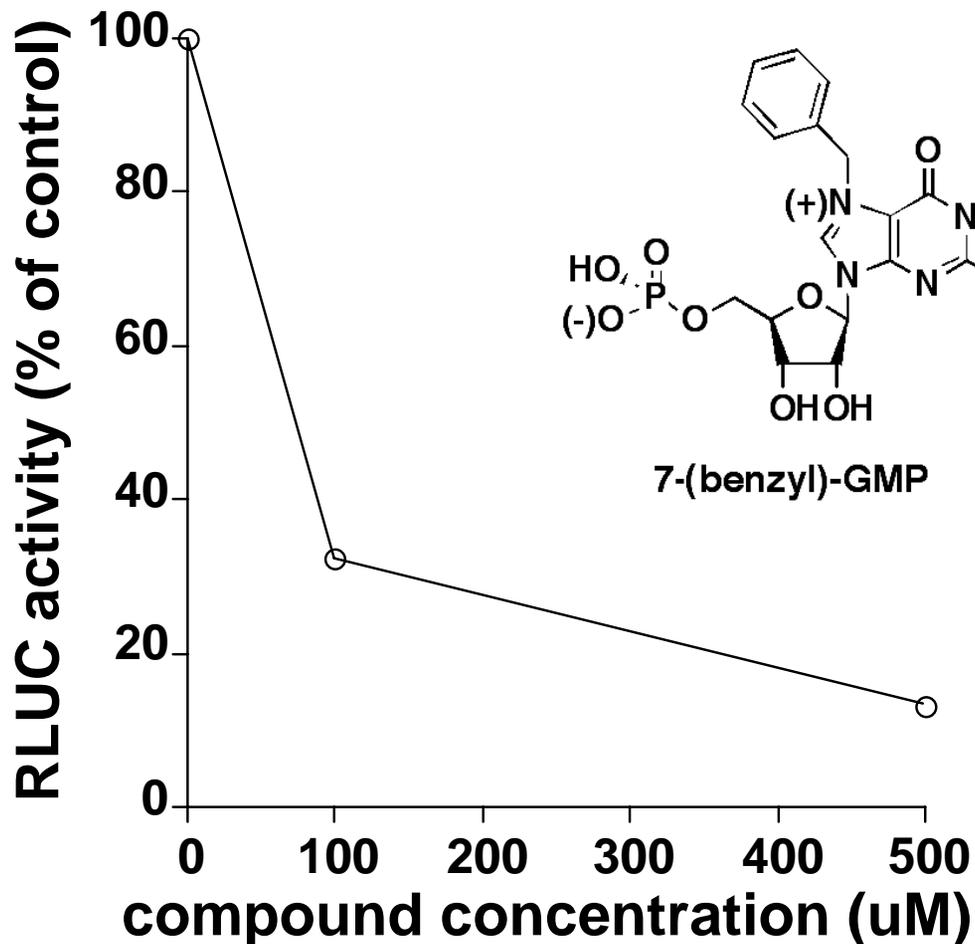


Wagner

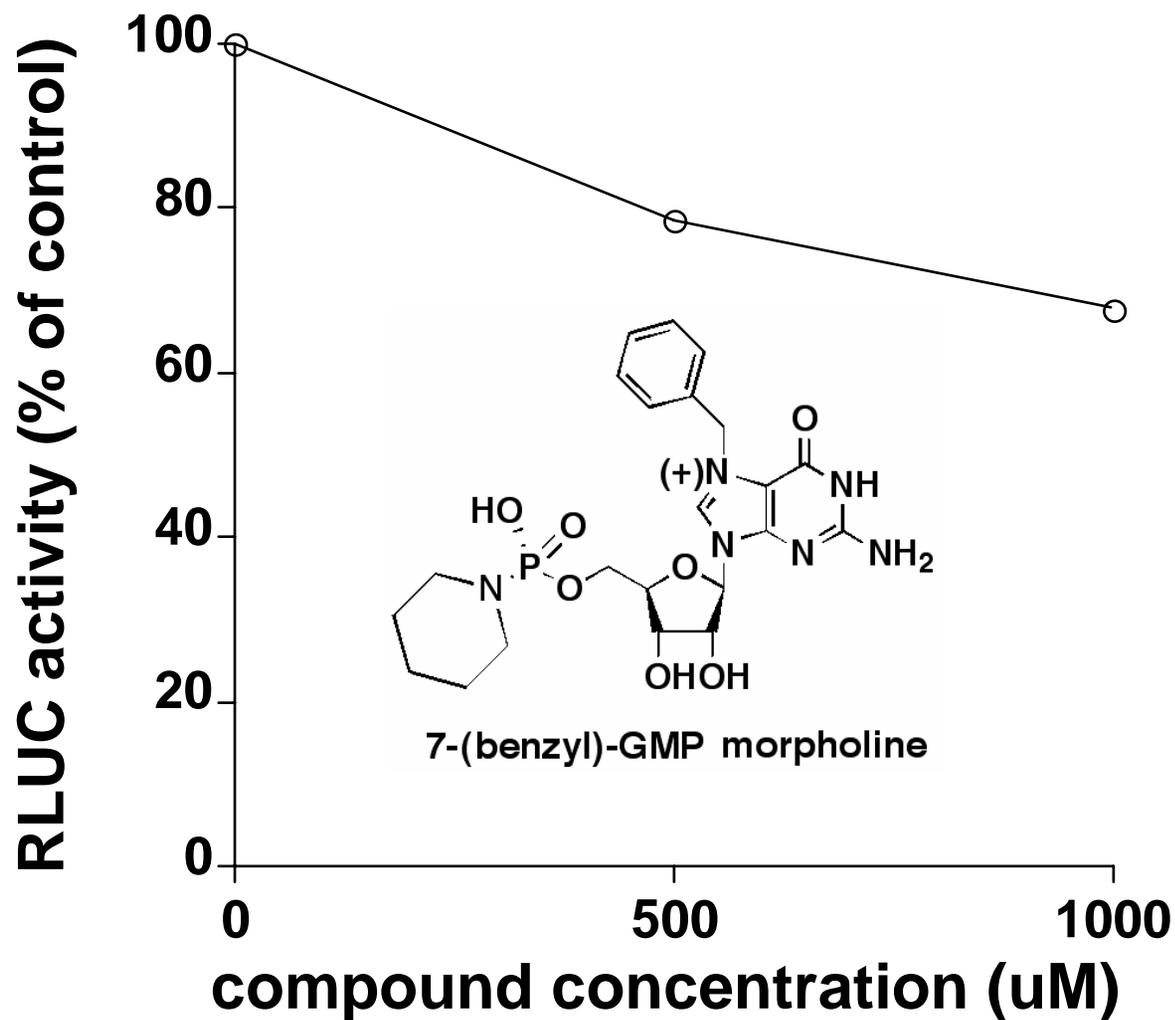
# Translation speedometer



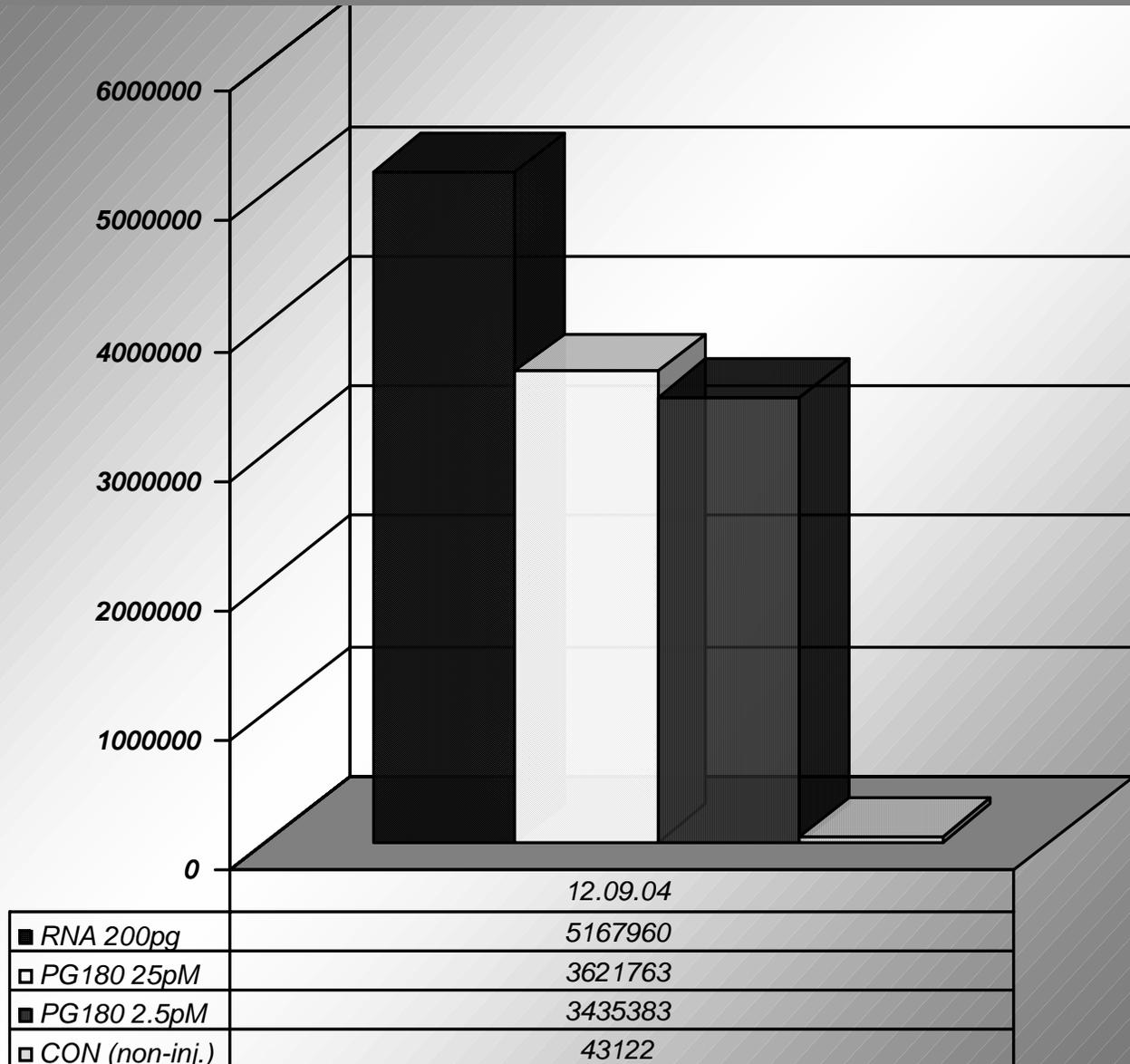
# Does it work in a test tube?



# Does it work in an intact cell?

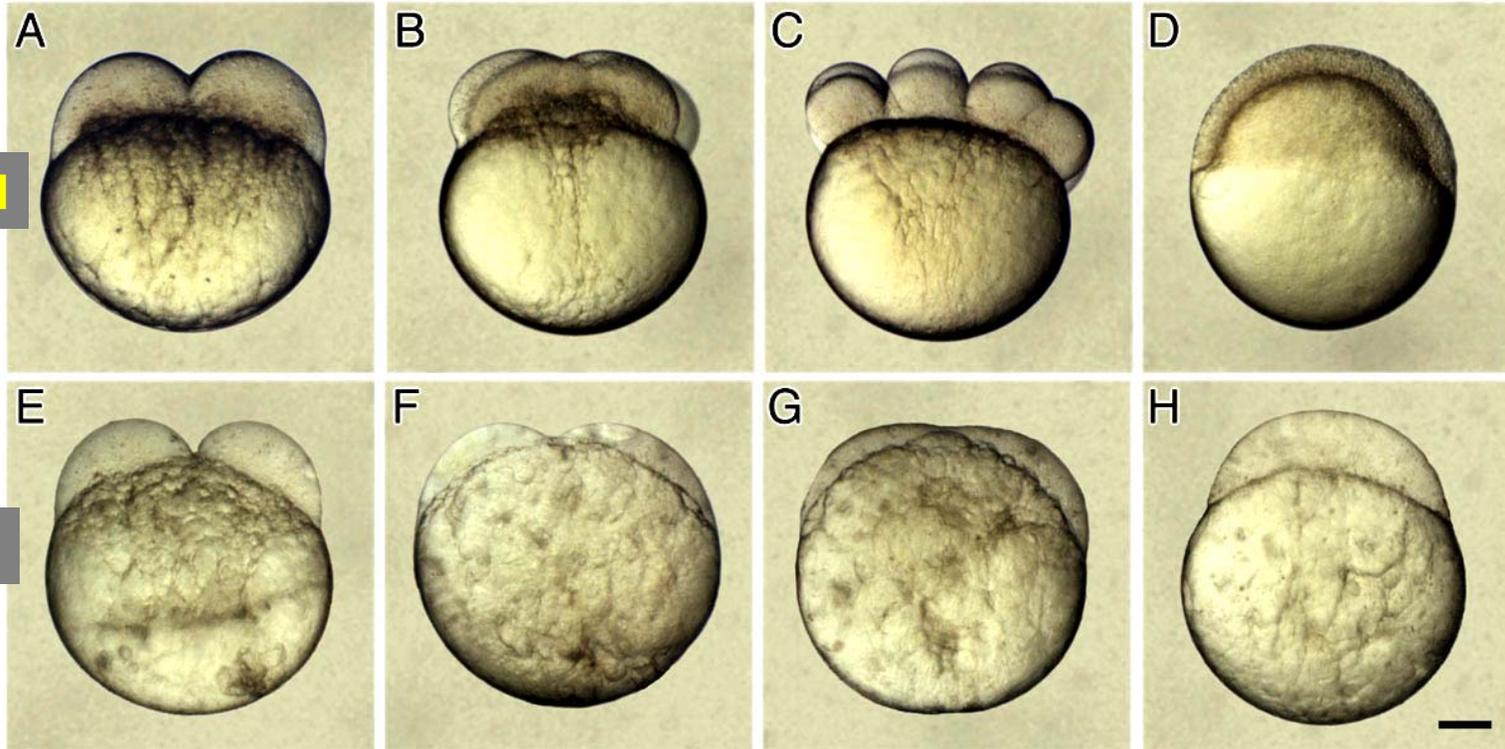


# Does it work in an intact organism? Zebrafish



# Does it disturb development of the zebrafish embryo?

Lead compound



cycloheximide

# What's next?

- **Patent filed**
- **Modify to increase potency**
- **Preclinical Testing**
- **Transfer to private sector partner**
- **R and D**
- **Phase 1, 2 and 3 trials**
- **Rx**

**Vitaly Polunovsky**

**Rick Wagner**

**Phalguni Ghosh**

**Mark Peterson**

**Alexey Benyumov**

**Svetlana Avdulov**

**J. Carlos Manivel**

**Shunan Li**

**Van Michalek**

**David Burrichter**

**David Perlman**

**Douglas Yee**

**Robert Kratzke**

**O. Larsson**

**Nahum Sonenberg (McGill, Montreal)**

